

# An Update on Randomized Clinical Trials in Gastric Cancer



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## KEYWORDS

- Esophageal cancer • Randomized clinical trial • Surgery • Chemotherapy
- Neoadjuvant therapy • Adjuvant therapy • Lymphadenectomy

## KEY POINTS

- There is no difference in oncologic outcomes comparing transhiatal with transthoracic esophagectomy.
- Nasogastric tubes assist in decreasing perioperative complications.
- Preoperative chemotherapy trials are difficult to evaluate because studies have examined squamous cell carcinoma versus adenocarcinoma and inconsistently included gastro-esophageal junction and gastric cardia tumors.
- Standard of care in Europe includes preoperative cisplatin and 5-fluoracil; however, ongoing studies are needed to study the subgroups of patients who benefit most from neoadjuvant chemotherapy.
- Randomized trials of preoperative radiation therapy have not increased resectability rates; a few recent trials show variable results in survival and pathologic complete responses with preoperative chemoradiotherapy.

## SURGICAL MANAGEMENT

The surgical approach to esophageal cancer involves either transhiatal or transthoracic esophagectomy. Hulscher and colleagues<sup>1</sup> randomized 220 patients with middle or distal esophageal cancer to either transhiatal or transthoracic esophagectomy. Original results revealed no difference in R0 resection rates, although the lymph node retrieval was significantly higher in the transthoracic group (31 vs 16;  $P < .001$ ).

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Disclosures: None.

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Surg Oncol Clin N Am 26 (2017) 621–645

<http://dx.doi.org/10.1016/j.soc.2017.05.003>

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Postoperative pulmonary complications and hospital duration of stay were higher in patients who underwent transthoracic esophagectomy. However, there were no differences in the perioperative mortality rates. Additionally, there were no differences in local or distant recurrence rates. Five-year survival analysis was comparable (34% and 36%;  $P = .71$ ). Three other phase III trials prospectively examined the outcomes of patients assigned to transhiatal and transthoracic esophagectomy, but no definitive conclusions could be reached owing to small sample sizes.<sup>2-4</sup>

Various reconstructive techniques have been addressed by 3 prospective, randomized, controlled trials. Gupta and colleagues<sup>5</sup> found a lower leak rate of 4.3% versus 20.8% ( $P = .03$ ) and stricture rate of 8.5% versus 29.2% ( $P = .02$ ) after a “novel” hand-sewn esophagogastric anastomosis compared with a standard hand-sewn anastomosis. Bhat and colleagues<sup>6</sup> found the anastomotic leak rate to be dramatically reduced after omental wrap of the esophagogastric anastomosis versus standard anastomosis (3.09% vs 14.43%;  $P = .005$ ). Tabira and colleagues<sup>7</sup> found no difference in anastomotic leak or postoperative nutritional status at 6 and 12 months after use of a slender gastric tube for reconstruction after esophagectomy when compared with a more generous gastric tube. Nederlof and colleagues<sup>8</sup> studied using an end-to-end (ETE) versus an end-to-side (ETS) esophagogastrostomy after esophageal cancer resection. This Dutch trial found the anastomotic stricture rate to be higher with the ETE anastomosis, but that the anastomotic leak rate, pulmonary complications, and duration of hospital stay were greater with an ETS anastomosis.

A number of trials addressed other surgical technique issues. A comparison of the Ivor-Lewis and Sweet esophagectomy techniques was performed for esophageal squamous cell carcinoma in 2015 by Li and colleagues<sup>9</sup>. Operative morbidity was higher with the Sweet technique, and Ivor-Lewis esophagectomy led to higher lymph node yield. A small institutional randomized trial also found that in prone versus decubitus positioning for minimally invasive esophagectomy, the prone positioning may decrease surgeon workload and lead to better ergonomic results.<sup>10</sup> A multicenter, open-label, randomized, controlled trial by Biere and colleagues<sup>11</sup> evaluated open esophagectomy versus minimally invasive esophagectomy. Short-term pulmonary complications were better with the minimally invasive technique, suggesting the usefulness of the minimally invasive approach over open esophagectomy in clinical practice and as an area for further research into long-term outcomes.

## PERIOPERATIVE OUTCOMES

Shackcloth and colleagues<sup>12</sup> completed a well-planned and executed study addressing the most appropriate use of nasogastric tubes (NGT) in the first 48 hours after esophagectomy. Thirty-four patients were randomized to NGT with continuous sump suction, single-lumen NGT with 4-hourly aspirations, or no NGT. The patients receiving continuous suction via the sump system spent significantly less time with a pH of less than 5.5 than either of the other 2 groups (4.3% vs 39.7% vs 40.3% [ $P = .007$ ]). Patients randomized to no NGT had significantly more pulmonary complications, 7 of 12 versus 4 of 22 ( $P = .02$ ), and required an NGT to be inserted in 7 of 12 cases. This study argues for the use of sump NGT in patients in the immediate perioperative period. A follow-up study by Mistry and colleagues<sup>13</sup> hypothesized that early removal of NGT would not adversely affect major pulmonary complications and anastomotic leak rates. This was confirmed in their single-center, parallel-group, open-label randomized trial of 150 patients.

Other recent trials have focused on perioperative interventions. The safety analysis of the Japan Clinical Oncology Group 9907 trial compared preoperative and

postoperative chemotherapy in 330 patients and found that operative and postoperative complications were similarly low.<sup>14</sup> Eicosapentaenoic acid (EPA)-enriched enteral nutrition (EN) was compared with standard EN and found to preserve fat-free mass better than standard nutrition and significantly attenuated stress response.<sup>15</sup> Several studies have shown that ghrelin can improve postoperative outcomes and minimize adverse events, even during the time of chemotherapy.<sup>16–18</sup> Synbiotics were similarly studied and found to decrease the inflammatory response after surgery.<sup>19,20</sup> Shyamsundar and colleagues<sup>21</sup> also looked at simvastatin as a method of decreasing biomarkers of inflammation, and they discovered that simvastatin was associated with the reduction of pulmonary and systemic injury after esophagectomy. Method of endoscopic resectional technique,<sup>22</sup> extent of lymph node resection,<sup>23</sup> thoracotomy versus thoracoscopy,<sup>24</sup> antibiotic bowel decontamination,<sup>25</sup> and prostaglandin E1 infusion<sup>26</sup> have been reported in “1c” trials without differences noted in primary endpoints.

## ADJUVANT THERAPY

### *Preoperative Chemotherapy*

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There are several challenges in evaluating preoperative chemotherapy trials for esophageal cancer, because studies have variably examined squamous cell carcinoma versus adenocarcinoma and inconsistently included gastroesophageal junction and gastric cardia tumors.

A study by Boonstra and colleagues<sup>27</sup> studied 171 patients with squamous cell carcinoma administered cisplatin and etoposide neoadjuvant chemotherapy. Overall survival was more favorable in the chemotherapy arm compared with patients who immediately went to surgery (5-year survival 26% vs 17%;  $P = .03$ ). The US Intergroup 0113 trial<sup>28</sup> randomized patients to receive perioperative cisplatin and 5-fluoracil (5-FU) or surgery alone. There were no differences in overall median or 3-year survival. Long-term follow-up confirmed these results, although a subgroup analysis revealed that patients with R1 resection seemed to benefit from postoperative chemoradiotherapy.<sup>29</sup> In contrast with the Intergroup trial, the Medical Research Council Oesophageal Working Group<sup>30,31</sup> found that preoperative cisplatin and 5-FU (at a lesser cisplatin dose of 160 mg/m<sup>2</sup> compared with the 450 mg/m<sup>2</sup> used in the Intergroup trial) conferred a survival advantage (23% vs 17%;  $P = .03$ ), likely from an increased rate of R0 resections (60% vs 54%). The Medical Research Council study had a larger sample size of 467 patients and a greater number of patients who received chemotherapy going on to surgery (92% vs 80% in the Intergroup trial). The Medical Research Council preliminarily reported the results of neoadjuvant randomized trial OEO5, comparing 2 cycles of cisplatin and 5-FU with 4 cycles of epirubicin, cisplatin, and capecitabine in 897 patients. There was no survival benefit with more chemotherapy.<sup>32</sup>

Several key trials grouped together distal esophagus, gastroesophageal junction, and gastric cancers in their studies. The Cunningham trial<sup>33</sup> (of which 26% of patients had distal esophagus or gastroesophageal junction tumors) randomized patients to perioperative epirubicin, cisplatin, and 5-FU or surgery alone. Chemotherapy improved 5-year overall survival (36% vs 23%;  $P = .009$ ). Yehou and colleagues<sup>34</sup> randomized 234 patients to immediate surgery or to perioperative cisplatin and 5-FU. The 5-year survival (38% vs 24%;  $P = .02$ ) and R0 resection rates (84% vs 73%,  $P = .04$ ) were better in the chemotherapy group. However, a European Organisation for Research and Treatment of Cancer trial by Schuhmacher and colleagues<sup>35</sup> found almost equivalent 2-year overall survival rates (70% for surgery alone vs 73% for cisplatin and 5-FU) in T3 and T4 tumors.

The standard of care in Europe for the management of esophageal cancer includes preoperative cisplatin and 5-FU. However, ongoing studies are needed to study the subgroups of patients who benefit most from neoadjuvant chemotherapy.

### ***Preoperative Radiotherapy and Chemoradiotherapy***

Randomized trials of preoperative radiation therapy alone have not increased resectability rates.<sup>36–41</sup> Mei and colleagues<sup>36</sup> reported no difference in the local failure rate, although Gignoux and colleagues<sup>37</sup> noticed a lower local failure rate with preoperative radiation (46% vs 67%;  $P = .045$ ). Nygaard and colleagues<sup>38</sup> observed an improvement in 3-year survival (18% vs 5%;  $P = .009$ ); however, some of these patients received chemotherapy. Therefore, preoperative radiation therapy alone has not been shown to improve survival endpoints consistently.

There are a few recent randomized trials that show variable results in survival and pathologic complete responses with preoperative chemoradiotherapy. These trials were limited by low statistical power, inadequacy of chemotherapy doses delivered, or unusually high postoperative mortality.<sup>42–49</sup> The CROSS trial (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) by van Hagen and colleagues<sup>50</sup> established preoperative chemoradiotherapy as standard of care in Western countries. The study randomized 366 patients with esophageal or gastroesophageal junction squamous cell carcinoma or adenocarcinoma to carboplatin at an area under the curve of 2 mg/mL per minute and paclitaxel 50 mg/m<sup>2</sup> once weekly for 5 weeks with concurrent radiotherapy (1.8 Gy daily to 41.4 Gy in 23 fractions) followed by surgery or surgery alone. There were no differences in perioperative outcomes (including postoperative mortality, <4%), and grade 3 or 4 toxicity was only seen in 13% of patients. R0 resection rates were achieved in 92% of patients versus 69% of patients in the surgery group ( $P < .001$ ). Median survival increased from 24 to 49 months (hazard ratio, 0.0657;  $P = .003$ ).

### ***Postoperative Chemotherapy***

The Japanese Oncology Group has evaluated postoperative chemotherapy in several randomized trials and found no survival benefit.<sup>51–53</sup> However, Iizuka and colleagues<sup>52</sup> noticed a trend toward, though not statistically significant, improvement in disease-free survival for node-positive patients who received adjuvant chemotherapy (53% vs 35%;  $P = .06$ ). Hence, survival may be prolonged in patients who had an R0 resection and lymph node–positive disease, but data are limited.

### ***Postoperative Radiotherapy and Chemoradiotherapy***

No improvement in survival was noticed in 2 randomized trials of adjuvant radiotherapy. Teniere and colleagues<sup>54</sup> gave 221 patients with squamous cell carcinoma 45 to 55 Gy and observed no impact on survival. Fok and colleagues<sup>55</sup> administered radiation to patients with squamous cell carcinomas and adenocarcinomas undergoing curative or palliative resections; there was no improvement in local control or median survival. Additionally, 20% of the Intergroup 0116 trial's<sup>56</sup> 603 patients had gastroesophageal junction adenocarcinoma. Patients who received postoperative chemoradiation had an increase in overall survival (50% vs 41%;  $P = .005$ ), especially the group of patients who were HER2 status negative.<sup>57</sup>

### ***Definitive Radiotherapy and Chemoradiotherapy Versus Surgery***

There are only 2 trials that directly compare nonoperative treatment (one with radiation alone and another with chemoradiation) with surgery.<sup>58,59</sup> It is difficult to draw

conclusions about these 2 studies because they are limited by low statistical power and short follow-up.

### **Radiotherapy Versus Chemoradiotherapy**

There are 6 randomized trials comparing radiation with chemoradiation.<sup>38,60–66</sup> However, these trials are difficult to compare because they include variable doses of radiation and systemic chemotherapy with different sequencing of therapies. An analysis of the pooled data<sup>67</sup> from these trials reported a significant local control and survival benefit at 1 year for chemoradiation over radiation alone, although chemoradiation predictably increased side effects. The Eastern Cooperative Oncology Group's EST-1282 trial<sup>65</sup> also demonstrated a median overall survival benefit (15 months vs 9 months;  $P = .04$ ) for patients receiving chemoradiation; however, there was no improvement in 5-year overall survival. This study was confounded by 50% of the patients in each arm undergoing surgery after radiation therapy by individual investigator's choice. The Radiation Therapy Oncology Group 85-01 Intergroup Trial reported by Herskovic and colleagues<sup>61</sup> and Al-Sarraf and colleagues<sup>63</sup> examined patients who received cisplatin and 5-FU chemotherapy with 50 Gy radiation compared with patients receiving 64 Gy radiation alone. There was improved 5-year survival in patients who received chemoradiation (27% vs 0%;  $P < .0001$ ).<sup>49</sup>

### **Surgery After Chemoradiotherapy**

A French study and a separate German study examined whether surgery is required after chemoradiotherapy. In the FFCD 9102 trial (Fédération Française de Cancérologie Digestive 9102),<sup>68,69</sup> 444 patients with clinically resectable T3 or T4 N0 or 1 and M0 esophageal squamous cell carcinoma or adenocarcinoma all received 5-FU, cisplatin, and 46 Gy at 2 Gy per day or a split course with 15 Gy in weeks 1 and 3. Those patients who demonstrated a partial response were randomized to surgery versus additional chemoradiation. There was no difference in 2-year survival (34% vs 40%;  $P = .44$ ) or median survival (17.7 months vs 19.3 months). These data suggest that patients with squamous cell carcinoma do not benefit from surgical intervention in lieu of continuing chemoradiation. A separate analysis showed that standard course radiation improved 2-year progression free survival compared with split course radiation (77% vs 57%;  $P = .002$ ).

The German trial also did not show an improvement in survival in uT3 or T4 N0 or N1 and M0 disease.

Patients with squamous cell carcinoma of the esophagus undergoing surgery after definitive chemoradiation.<sup>70</sup> The German Oesophageal Cancer Study Group compared preoperative chemoradiation (3 cycles of 5-FU, leucovorin, etoposide, and cisplatin, followed by concurrent etoposide, cisplatin, plus 40 Gy followed by surgery vs the same chemotherapy regimen with 60–65 Gy with or without brachytherapy). The 3-year survival (31% vs 24%) was not significantly different. These 2 trials confirm that it is reasonable from an oncologic perspective to treat patients with squamous cell carcinoma with definitive chemoradiation.

## **SUMMARY OF LEVEL IA EVIDENCE**

### **Randomized, Controlled Trials in Esophageal Cancer**

#### **Clinical study 1**

Li B, Xiang J, Zhang Y, et al. Comparison of Ivor-Lewis vs Sweet esophagectomy for esophageal squamous cell carcinoma: a randomized clinical trial. *JAMA Surg* 2015;150(4):292–8.

| No. Patients<br>Randomized | Study Groups                                    | Stratification | Significance<br>Demonstrated | % Change Identified in Trial |
|----------------------------|-------------------------------------------------|----------------|------------------------------|------------------------------|
| 300                        | Ivor Lewis,<br>N = 150<br><br>Sweet,<br>N = 150 | None           | Yes, operative<br>morbidity  | 30% vs 41.3% ( $P = .04$ )   |

**Hypothesis** To determine whether Ivor-Lewis esophagectomy is associated with increased postoperative complications compared with the Sweet procedure.

**Published abstract**

**Background** Sweet esophagectomy is performed widely in China, whereas the Ivor-Lewis procedure, with potential benefit of an extended lymphadenectomy, is limitedly conducted owing to concern for a higher risk for morbidity. Thus, the role of the Ivor-Lewis procedure for thoracic esophageal cancer needs further investigation.

**Methods** A randomized clinical trial was conducted from May 2010 to July 2012 at Fudan University Shanghai Cancer Center, Shanghai, China, of 300 patients with resectable squamous cell carcinoma in the middle and lower thirds of the thoracic esophagus. An intent-to-treat analysis was performed. Patients were assigned randomly to undergo either the Ivor-Lewis ( $n = 150$ ) or Sweet ( $n = 150$ ) esophagectomy. The primary outcome of this clinical trial was operative morbidity (any surgical or nonsurgical complications). Secondary outcomes included oncologic efficacy (number of lymph nodes resected and positive lymph nodes), postoperative mortality (30-day and in-hospital mortality), and patient discharge.

**Results** Resection without macroscopic residual (R0/R1) was achieved in 149 of 150 patients in each group. Although there was no difference between the 2 groups regarding the incidence of each single complication, a significantly higher morbidity rate was found in the Sweet group (62 of 150 [41.3%]) than in the Ivor-Lewis group (45 of 150 [30%];  $P = .04$ ). More patients in the Sweet group (8 of 150 [5.3%]) underwent reoperations than in the Ivor-Lewis group (1 of 150 [0.7%]) ( $P = .04$ ). The median duration of hospital stay was 18 days in the Sweet group versus 16 days in the Ivor-Lewis group ( $P = .002$ ). Postoperative mortality rates in the Ivor-Lewis (1 of 150) and Sweet (3 of 150) groups were 0.7% and 2.0%, respectively ( $P = .25$ ). More lymph nodes were removed during Ivor-Lewis esophagectomy than during the Sweet procedure (22 vs 18;  $P < .001$ ).

**Conclusions** The early results of this study demonstrate that the Ivor-Lewis procedure can be performed with lower rates of postoperative complications and more lymph node retrieval. Ivor-Lewis and Sweet esophagectomies are both safe procedures with low operative mortalities.

**Editor's summary and comments** This clinical trial evaluated 2 techniques for esophagectomy, Ivor-Lewis compared with the Sweet procedure. Higher morbidity was found with the Sweet group (41.3% vs 30%;  $P = .04$ ). The Sweet group had more reoperations, greater duration of stay, and fewer lymph nodes removed. This study leads to a recommendation of Ivor-Lewis esophagectomy to reduce postoperative complications and increase lymph node retrieval.

**Clinical study 2**

Takata A, Takiguchi S, Miyazaki Y, et al. Randomized phase II study of the anti-inflammatory effect of ghrelin during the postoperative period of esophagectomy. *Ann Surg* 2015;262(2):230–6.

| No. Patients Randomized | Study Groups                       | Stratification | Significance Demonstrated                             | % Change Identified in Trial          |
|-------------------------|------------------------------------|----------------|-------------------------------------------------------|---------------------------------------|
| 40                      | Ghrelin, n = 20<br>Placebo, n = 20 | None           | Yes, systemic inflammatory response syndrome duration | 3.0 d vs 6.7 d<br>( <i>P</i> = .0062) |

**Hypothesis** Ghrelin reduces systemic inflammatory response syndrome (SIRS) duration after esophagectomy.

#### Published abstract

**Background** Esophagectomy for esophageal cancer is highly invasive and leads to prolonged SIRS duration and postoperative complications. Ghrelin has multiple effects, including antiinflammatory effects.

**Methods** Forty patients undergoing esophagectomy were assigned randomly to either the ghrelin group (*n* = 20), which received continuous infusion of ghrelin (0.5 µg/kg/h) for 5 days, or the placebo group (*n* = 20), which received pure saline for 5 days. The primary endpoint was SIRS duration. The secondary endpoints were the incidence of postoperative complications, time of a negative nitrogen balance, changes in body weight and composition, and levels of inflammatory markers, including C-reactive protein and interleukin (IL)-6.

**Results** The ghrelin group had a shorter SIRS duration and lower C-reactive protein and IL-6 levels than did the placebo group. The incidence of pulmonary complications was lower in the ghrelin group than in the placebo group, whereas other complications did not differ between the groups. Although time of the negative nitrogen balance was shorter in the ghrelin group than in the placebo group, changes in total body weight and lean body weight did not differ significantly.

**Conclusions** Postoperative ghrelin administration was effective for inhibiting inflammatory mediators and improving the postoperative clinical course of patients with esophageal cancer.

| No. Patients Randomized | Study Groups                       | Stratification | Significance Demonstrated | % Change Identified in Trial    |
|-------------------------|------------------------------------|----------------|---------------------------|---------------------------------|
| 67                      | Decubitus, n = 32<br>Prone, n = 35 | None           | Yes<br>Symptom scale      | 6.29 vs 3.13 ( <i>P</i> < .001) |

**Editor's summary and comments** This prospective, randomized, placebo-controlled phase II institutional study from Japan studied the postoperative benefit of ghrelin administration. The duration of SIRS was significantly shorter with ghrelin administration. Studies with larger sample sizes and long-term outcomes will be of benefit to clarifying the full impact of ghrelin in postesophagectomy patients.

#### Clinical study 3

Shen Y, Feng M, Tan L, et al. Thoracoscopic esophagectomy in prone versus decubitus position: ergonomic evaluation from a randomized and controlled study. *Ann Thorac Surg* 2014;98(3):1072–8.

**Hypothesis** Prone positioning may provide better ergonomics.

**Published abstract**

**Background** The prone position (PP) and decubitus position (DP) have both been used for thoracoscopic esophagectomy. However, which of these positions is ergonomically better for the operating surgeon is unknown. In this randomized, controlled trial (NCT01144325), we aimed to assess the surgeon’s physical and mental stress in operating on patients in the PP compared with that in the DP.

**Methods** From October 2012 to June 2013, 67 consecutive patients who underwent a 3-stage, minimally invasive esophagectomy were assigned randomly to the DP or the PP during the thoracic stage. The same senior surgeon performed all operations. Objectively, the surgeon’s spontaneous eye blink rate was recorded during thoracoscopic esophagectomy. Subjectively, the physician’s musculoskeletal symptoms were rated on a scale ranging from 1 (uninfluenced) to 10 (maximum fatigue). Clinical characteristics, including patient demographics and operative features of the 2 patient groups, were compared statistically.

**Results** There were 35 patients in the PP group and 32 in the DP group. The 2 groups were comparable in patient demographics. The thoracic stage of the operation was longer in the DP group than in the PP group ( $87 \pm 24$  minutes vs  $68 \pm 22$  minutes;  $P < .001$ ), and the volume of blood loss was higher ( $89 \pm 18$  mL vs  $67 \pm 16$  mL;  $P < .001$ ). The surgeon’s eye blink rate at the end of thoracic stage decreased more from baseline in the DP group than in the PP group ( $3.0 \pm 1.4$  blinks/min vs  $1.2 \pm 0.9$  blinks/min;  $P < .001$ ), and the surgeon’s symptom scale score was higher after operation with the patient in the DP than in the PP ( $6.29 \pm 1.54$  vs  $3.13 \pm 2.82$ ;  $P < .001$ ). No conversion to open thoracotomy was recorded in either group.

**Conclusions** Thoracoscopic esophagectomy in the PP provided less workload and better ergonomic results than the DP. Further study based on a larger number of patients is required to confirm these findings.

**Editor’s summary and comments** This small, institutional, randomized trial of prone versus decubitus positioning for esophagectomy was designed to evaluate the surgeon’s mental and physical stress with each position. The musculoskeletal symptom scale was significantly higher with decubitus over prone positioning, suggesting PP may decrease surgeon workload and lead to better ergonomic results.

| No. Patients Randomized | Study Groups                          | Stratification | Significance Demonstrated                          | % Change Identified in Trial                                                                       |
|-------------------------|---------------------------------------|----------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 42                      | Synbiotics, n = 21<br>Control, n = 21 | None           | Yes<br>Mesenteric lymph node samples<br>Bacteremia | Mesenteric lymph node microorganisms: 3 vs 10 ( $P = .035$ )<br>Bacteremia: 4 vs 12 ( $P = .025$ ) |

**Clinical study 4**

Yokoyama Y, Nishigaki E, Abe T, et al. Randomized clinical trial of the effect of peri-operative synbiotics versus no synbiotics on bacterial translocation after oesophagectomy. *Br J Surg.* 2014;101(3):189–99.

**Hypothesis** Perioperative synbiotics reduce postoperative bacteremia.

#### Published abstract

**Background** The impact of perioperative synbiotics on bacterial translocation and subsequent bacteremia after esophagectomy is unclear. This study investigated the effect of perioperative synbiotic administration on the incidence of bacterial translocation to mesenteric lymph nodes (MLNs) and the occurrence of postoperative bacteremia.

**Methods** Patients with esophageal cancer were randomized to receive perioperative synbiotics or no synbiotics (control group). MLNs were harvested from the jejunal mesentery before dissection (MLN-1) and after the restoration of digestive tract continuity (MLN-2). Blood and feces samples were taken before and after operation. Microorganisms in each sample were detected using a bacterium-specific ribosomal RNA-targeted reverse transcriptase-quantitative polymerase chain reaction method.

**Results** Some 42 patients were included. There was a significant difference between the 2 groups in detection levels of microorganisms in the MLN-1 samples. Microorganisms were more frequently detected in MLN-2 samples in the control group than in the synbiotics group (10 of 18 vs 3 of 18;  $P = .035$ ). In addition, bacteremia detected using reverse transcriptase-quantitative polymerase chain reaction 1 day after surgery was more prevalent in the control group than in the synbiotics group (12 of 21 vs 4 of 21;  $P = .025$ ). Neutrophil counts on postoperative days 1, 2, and 7 were all significantly higher in the control group than in the synbiotics group.

**Conclusion** Perioperative use of synbiotics reduces the incidence of bacteria in the MLNs and blood. These beneficial effects probably contribute to a reduction in the inflammatory response after esophagectomy.

**Editor's summary and comments** This small, randomized trial studied the impact of perioperative synbiotics in patients with esophageal cancer after esophagectomy. The detection of microorganisms in MLNs and bacteremia were significantly less in the group that received synbiotics, suggesting a future role for future studies of synbiotics in the reduction of inflammatory response after esophagectomy.

#### Clinical study 5

Shyamsundar M, McAuley DF, Shields MO, et al. Effect of simvastatin on physiological and biological outcomes in patients undergoing esophagectomy: a randomized placebo-controlled trial. *Ann Surg* 2014;259(1):26–31.

| No. Patients Randomized | Study Groups                           | Stratification | Significance Demonstrated                            | % Change Identified in Trial |
|-------------------------|----------------------------------------|----------------|------------------------------------------------------|------------------------------|
| 31                      | Simvastatin, n = 15<br>Placebo, n = 16 | None           | Yes, pulmonary dead space at 6 h after esophagectomy | 94.7 h vs 113.9 h            |

**Hypothesis** Simvastatin improves physiologic and biological outcomes in patients undergoing esophagectomy.

**Published abstract**

**Background** Single-lung ventilation during esophagectomy is associated with inflammation, alveolar epithelial and systemic endothelial injury, and the development of acute lung injury. Statins that modify many of the underlying processes are a potential therapy to prevent acute lung injury.

**Methods** We conducted a randomized, double-blind, placebo-controlled trial in patients undergoing esophagectomy. Patients received simvastatin 80 mg or placebo enterally for 4 and 7 days postoperatively. The primary endpoint was pulmonary dead space (Vd/Vt) at 6 hours after esophagectomy or before extubation. Inflammation was assessed by plasma cytokines and intraoperative exhaled breath condensate pH; alveolar type 1 epithelial injury was assessed by plasma receptor for advanced glycation end products and systemic endothelial injury by the urine albumin-creatinine ratio.

**Results** Thirty-nine patients were randomized; 8 patients did not undergo surgery and were excluded. Fifteen patients received simvastatin and 16 received placebo. There was no difference in Vd/Vt or other physiologic outcomes. Simvastatin resulted in a significant decrease in plasma monocyte chemoattractant protein 1 on day 3 and reduced exhaled breath condensate acidification. Plasma receptor for advanced glycation end products was significantly lower in the simvastatin-treated group, as was the urine albumin-creatinine ratio on postoperative day 7. Acute lung injury developed in 4 patients in the placebo group and no patients in the simvastatin group, although this difference was not statistically significant ( $P = .1$ ).

**Conclusions** In this proof-of-concept study, pretreatment with simvastatin in esophagectomy decreased biomarkers of inflammation as well as pulmonary epithelial and systemic endothelial injury.

**Editor's summary and comments** In this multicenter, randomized, double-blind, placebo-controlled trial from Japan, the effect of daikenchuto was studied in patients recovering from total gastrectomy. The mean time to bowel movement was significantly shorter in the daikenchuto group (94.7 hours vs 113.9 hours;  $P = .051$ ). This finding suggests a potential role for daikenchuto in the postoperative bowel recovery of total gastrectomy patients.

**Clinical study 6**

van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366(22):2074–84.

| No. Patients<br>Randomized | Study Groups                                                      | Stratification | Significance<br>Demonstrated                             | % Change Identified<br>in Trial                                                                                    |
|----------------------------|-------------------------------------------------------------------|----------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| 366                        | Chemoradiation<br>+ surgery, n = 178<br>Surgery alone,<br>n = 188 | None           | Yes, complete<br>resection<br>Median overall<br>survival | Complete resection:<br>92% vs 69% ( $P<.001$ )<br>Median overall survival:<br>49.4 mo vs 24.0 mo<br>( $P = .003$ ) |

**Hypothesis** Chemoradiation improves outcomes in resectable esophageal and junctional cancer.

### Published abstract

**Background** The role of neoadjuvant chemoradiotherapy in the treatment of patients with esophageal or esophagogastric junction cancer is not well-established. We compared chemoradiotherapy followed by surgery with surgery alone in this patient population.

**Methods** We randomly assigned patients with resectable tumors to receive surgery alone or weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg/mL/min) and paclitaxel (50 mg/m<sup>2</sup> body surface area) for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by surgery.

**Results** From March 2004 through December 2008, we enrolled 368 patients, 366 of whom were included in the analysis: 275 (75%) had adenocarcinoma, 84 (23%) had squamous cell carcinoma, and 7 (2%) had large-cell undifferentiated carcinoma. Of the 366 patients, 178 were randomly assigned to chemoradiotherapy followed by surgery, and 188 to surgery alone. The most common major hematologic toxic effects in the chemoradiotherapy–surgery group were leukopenia (6%) and neutropenia (2%); the most common major nonhematologic toxic effects were anorexia (5%) and fatigue (3%). Complete resection with no tumor within 1 mm of the resection margins (R0) was achieved in 92% of patients in the chemoradiotherapy–surgery group versus 69% in the surgery group ( $P < .001$ ). A pathologic complete response was achieved in 47 of 161 patients (29%) who underwent resection after chemoradiotherapy. Postoperative complications were similar in the 2 treatment groups, and in-hospital mortality was 4% in both. Median overall survival was 49.4 months in the chemoradiotherapy–surgery group versus 24.0 months in the surgery group. Overall survival was significantly better in the chemoradiotherapy–surgery group (hazard ratio, 0.657; 95% CI, 0.495–0.871;  $P = .003$ ).

**Conclusions** Preoperative chemoradiotherapy improved survival among patients with potentially curable esophageal or esophagogastric junction cancer. The regimen was associated with acceptable adverse-event rates. (Funded by the Dutch Cancer Foundation [KWF Kankerbestrijding]; Netherlands Trial Register number, NTR487.)

**Editor's summary and comments** In this randomized trial, chemoradiotherapy (carboplatin, paclitaxel, and 41.4 Gy concurrent radiotherapy) followed by surgery was compared with surgery alone in patients with esophageal or esophagogastric junction cancer. The median overall survival was significantly better with preoperative chemoradiation compared with surgery alone.

### Clinical study 7

Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012;379(9829):1887–92.

| No. Patients Randomized | Study Groups                                       | Stratification | Significance Demonstrated | % Change Identified in Trial |
|-------------------------|----------------------------------------------------|----------------|---------------------------|------------------------------|
| 105                     | Minimally invasive surgery, n = 59<br>Open, n = 56 | None           | Yes, pulmonary infection  | 34% vs 12% ( $P = .005$ )    |

**Hypothesis** Minimally invasive esophagectomy reduces morbidity compared with open esophagectomy.

**Published abstract**

**Background** Surgical resection is regarded as the only curative option for resectable esophageal cancer, but pulmonary complications occurring in more than one-half of patients after open esophagectomy are a great concern. We assessed whether minimally invasive esophagectomy reduces morbidity compared with open esophagectomy.

**Methods** We conducted a multicenter, open-label, randomized, controlled trial at 5 study centers in 3 countries between June 1, 2009, and March 31, 2011. Patients aged 18 to 75 years with resectable cancer of the esophagus or gastroesophageal junction were randomly assigned via a computer-generated randomization sequence to undergo either open transthoracic or minimally invasive transthoracic-esophagectomy. Randomization was stratified by center. Patients, and investigators undertaking interventions, assessing outcomes, and analyzing data, were not masked to group assignment. The primary outcome was pulmonary infection within the first 2 weeks after surgery and during the whole stay in hospital. Analysis was by intention to treat. This trial is registered with the Netherlands Trial Register, NTR TC 2452.

**Results** We randomly assigned 56 patients to the open esophagectomy group and 59 to the minimally invasive esophagectomy group. In the open esophagectomy group, 16 patients (29%) had a pulmonary infection in the first 2 weeks compared with 5 (9%) in the minimally invasive group (relative risk, 0.30; 95% CI, 0.12–0.76;  $P = .005$ ). In the open esophagectomy group, 19 patients (34%) had pulmonary infection in-hospital compared with 7 (12%) in the minimally invasive group (relative risk, 0.35; 95% CI, 0.16–0.78;  $P = .005$ ). For in-hospital mortality, 1 patient in the open esophagectomy group died from anastomotic leakage and 2 in the minimally invasive group from aspiration and mediastinitis after anastomotic leakage.

**Conclusions** These findings provide evidence for the short-term benefits of minimally invasive esophagectomy for patients with resectable esophageal cancer.

**Editor's summary and comments** In this multicenter, open-label, randomized, controlled trial, patients were assigned to open esophagectomy or minimally invasive esophagectomy. Short-term pulmonary complications were better with the minimally invasive technique, suggesting that the usefulness of this the minimally invasive approach over open esophagectomy.

| No. Patients<br>Randomized | Study Groups                          | Stratification | Significance<br>Demonstrated | % Change Identified<br>in Trial            |
|----------------------------|---------------------------------------|----------------|------------------------------|--------------------------------------------|
| 64                         | Synbiotics, n = 30<br>Control, n = 34 | None           | Yes, infection               | Infection: 10% vs 29.4%<br>( $P = .0676$ ) |

**Clinical study 8**

Tanaka K, Yano M, Motoori M, et al. Impact of perioperative administration of synbiotics in patients with esophageal cancer undergoing esophagectomy: a prospective randomized controlled trial. *Surgery* 2012;152(5):832–42.

**Hypothesis** Preoperative synbiotics are clinically beneficial.

**Published abstract**

**Background** The clinical value of synbiotics in patients undergoing esophagectomy remains unclear. This study investigated the effects of synbiotics on intestinal microflora and surgical outcomes in a clinical setting.

**Methods** We studied 70 patients with esophageal cancer who were scheduled to undergo esophagectomy. They were randomly allocated to 2 groups: 1 group received synbiotics before and after surgery, and the other did not. Fecal microflora and organic acid concentrations were determined. Postoperative infections, abdominal symptoms, and duration of SIRS were recorded.

**Results** Of the patients, 64 completed the trial (synbiotics, 30; control, 34). The counts of beneficial bacteria and harmful bacteria in the group given synbiotics were significantly larger and smaller, respectively, than those in the control group on postoperative day 7. The concentrations of total organic acid and acetic acid were higher in the synbiotics group than in the control group ( $P < .01$ ), and the intestinal pH in the synbiotics group was lower than that in the control ( $P < .05$ ) on postoperative day 7. The rate of infections was 10% in the synbiotics group and 29.4% in the control group ( $P = .0676$ ). The duration of SIRS in the synbiotics group was shorter than in the control group ( $P = .0057$ ). The incidence of interruption or reduction of EN by abdominal symptoms was 6.7% in the synbiotics group and 29.4% in the control group ( $P = .0259$ ).

**Conclusion** Perioperative administration of synbiotics in patients with esophagectomy is useful because they suppress excessive inflammatory response and relieve uncomfortable abdominal symptoms through the adjustment of the intestinal microfloral environment.

**Editor's summary and comments** In this small, randomized trial, patients who received synbiotics had significantly reduced rates of infections, SIRS duration, and interruption or reduction of EN by abdominal symptoms. This study indicates the short-term benefits of synbiotics in the postoperative period after esophagectomy.

| No. Patients<br>Randomized | Study Groups                       | Stratification | Significance<br>Demonstrated | % Change Identified<br>in Trial                    |
|----------------------------|------------------------------------|----------------|------------------------------|----------------------------------------------------|
| 42                         | Ghrelin, n = 21<br>Placebo, n = 21 | None           | Yes, oral calorie<br>intake  | 18.2 kcal/kg/d vs<br>12.7 kcal/kg/d ( $P = .001$ ) |

**Clinical study 9**

Hiura Y, Takiguchi S, Yamamoto K, et al. Effects of ghrelin administration during chemotherapy with advanced esophageal cancer patients: a prospective, randomized, placebo-controlled phase 2 study. *Cancer* 2012;118(19):4785–94.

**Hypothesis** Ghrelin administration minimizes side effects of cisplatin-based chemotherapy in patients with esophageal cancer.

**Published abstract**

**Background** Cisplatin reduces plasma ghrelin levels through the 5-hydroxytryptamine receptor. This may cause cisplatin-induced gastrointestinal disorders and hinders the continuation of chemotherapy. The authors of this report conducted a prospective, randomized phase II trial to evaluate the effects of exogenous ghrelin during cisplatin-based chemotherapy.

**Methods** Forty-two patients with esophageal cancer who were receiving cisplatin-based neoadjuvant chemotherapy were assigned to either a ghrelin group (n = 21) or a placebo group (n = 21). They received either intravenous infusions of synthetic human ghrelin (3 µg/kg) or saline twice daily for 1 week with cisplatin administration. The primary endpoint was changes in oral calorie intake, and the secondary endpoints were chemotherapy-related adverse events; appetite visual analog scale scores; changes in gastrointestinal hormones and nutritional status, including rapid turnover proteins, and quality of life estimated with the European Organization for Research and Treatment of Cancer Quality of Life core questionnaire.

**Results** Two patients were excluded from the final analysis: 1 patient suspended ghrelin administration because of excessive diaphoresis and another patient in the placebo group failed to monitor the self-questionnaire. Food intake and appetite visual analog scale scores were significantly higher in the ghrelin group than in the placebo group ( $18.2 \pm 5.2$  kcal/kg/d vs  $12.7 \pm 3.4$  kcal/kg/d [ $P = .001$ ] and  $6.2 \pm 0.9$  vs  $4.1 \pm 0.9$  [ $P < .0001$ ], respectively). Patients in the ghrelin group had fewer adverse events during chemotherapy related to anorexia and nausea than patients in the control group. Significant deterioration was noted after chemotherapy in the placebo group in quality of life scores, appetite, nausea and vomiting, and global health status.

**Conclusions** Short-term administration of exogenous ghrelin at the start of cisplatin-based chemotherapy stimulated food intake and minimized adverse events.

**Editor’s summary and comments** Cisplatin reduces plasma ghrelin levels through the 5-hydroxytryptamine receptor. Forty-two patients undergoing neoadjuvant cisplatin-based chemotherapy were randomized to receive ghrelin versus placebo. Patients receiving ghrelin were found to have a significantly higher caloric intake. This study suggests the importance of ghrelin in minimizing cisplatin-based chemotherapy side effects.

| No. Patients<br>Randomized | Study Groups                                                                                | Stratification | Significance<br>Demonstrated | % Change<br>Identified in Trial |
|----------------------------|---------------------------------------------------------------------------------------------|----------------|------------------------------|---------------------------------|
| 195                        | Omeage-3 fatty acids,<br>n = 66<br>Standard enteral nutrition,<br>n = 63<br>Control, N = 66 | None           | No                           | None                            |

**Clinical study 10**

Sultan J, Griffin SM, Di Franco F, et al. Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. *Br J Surg* 2012;99(3):346–55.

**Hypothesis** Perioperative omega-3 fatty acid (O3-FA)–supplemented EN improves clinical outcomes.

**Published abstract**

**Background** Esophagogastric cancer surgery is immunosuppressive. This may be modulated by O-3FAs. The aim of this study was to assess the effect of perioperative O-3FAs on clinical outcome and immune function after surgery for esophagogastric cancer.

**Methods** Patients undergoing subtotal esophagectomy and total gastrectomy were recruited and allocated randomly to an O-3FA enteral immunoenhancing diet (IED) or standard enteral nutrition for 7 days before and after surgery, or to postoperative supplementation alone (control group). Clinical outcome, fatty acid concentrations, and HLA-DR expression on monocytes and activated T lymphocytes were determined before and after operation.

**Results** Of 221 patients recruited, 26 were excluded. Groups (IED, 66; standard enteral nutrition, 63; control, 66) were matched for age, malnutrition, and comorbidity. There were no differences in morbidity ( $P = .646$ ), mortality ( $P = 1.000$ ), or duration of hospital stay ( $P = .701$ ) between the groups. The O-3FA concentrations were higher in the IED group after supplementation ( $P < .001$ ). The ratio of omega-6 fatty acid to O-3FA was 1.9:1, 4.1:1 and 4.8:1 on the day before surgery in the IED, standard enteral nutrition, and control groups, respectively ( $P < .001$ ). There were no differences between the groups in HLA-DR expression in either monocytes ( $P = .538$ ) or activated T lymphocytes ( $P = .204$ ).

**Conclusion** Despite a significant increase in plasma concentrations of O-3FA, immunonutrition with O-3FA did not affect overall HLA-DR expression on leukocytes or clinical outcome after surgery for esophagogastric cancer.

**Editor's summary and comments** The aim of this 3-arm, randomized study was to assess the effect of perioperative O-3FAs on clinical outcome and immune function after esophageal cancer surgery. Immunonutrition with O-3FAs did not affect clinical outcomes.

### Clinical study 11

Hirao M, Ando N, Tsujinaka T, et al. Influence of preoperative chemotherapy for advanced thoracic oesophageal squamous cell carcinoma on perioperative complications. *Br J Surg* 2011;98(12):1735–41.

| No. Patients<br>Randomized | Study Groups                                    | Stratification | Significance<br>Demonstrated | % Change Identified<br>in Trial |
|----------------------------|-------------------------------------------------|----------------|------------------------------|---------------------------------|
| 330                        | Postoperative, n = 166<br>Preoperative, n = 164 | None           | No                           | None                            |

**Hypothesis** Preoperative chemotherapy does not increase postoperative complications.

### Published abstract

**Background** The Japan Clinical Oncology Group 9907 trial has changed the standard of care for advanced thoracic esophageal cancer in Japan from postoperative chemotherapy to preoperative chemotherapy. The impact of preoperative chemotherapy on the risk of developing postoperative complications remains controversial. This article reports the safety analysis of Japan Clinical Oncology Group 9907, focusing on risk factors for postoperative complications.

**Methods** Patients were potentially randomized to either postoperative or preoperative chemotherapy followed by transthoracic esophagectomy with D2-3 lymphadenectomy. Chemotherapy consisted of 2 cycles of cisplatin and 5-FU. Clinical baseline data, intraoperative complications, postoperative complications, and in-

hospital mortality, collected on the case report forms in a predetermined format, were analyzed. Univariable and multivariable analyses were used to explore the risk of postoperative complications in relation to treatment group, age, sex, tumor depth, nodal metastasis, stage, and location.

**Results** Of 330 patients randomized, 166 were assigned to receive postoperative chemotherapy and 164 preoperative chemotherapy; 162 and 154 patients, respectively, underwent surgery. The incidence of intraoperative complications, postoperative complications and in-hospital mortality was similarly low in both groups. Multivariable analysis showed that age, sex, and tumor location were associated independently with an increase in postoperative complications, but preoperative chemotherapy was not.

**Conclusion** Preoperative chemotherapy does not increase the risk of complications or hospital mortality after surgery for advanced thoracicoesophageal cancer.

**Editor's summary and comments** This is the safety analysis of the Japan Clinical Oncology Group 9907 trial, comparing postoperative and preoperative chemotherapy in 330 randomized patients. Operative and postoperative complications were similarly low, indicating that preoperative chemotherapy does not affect short-term outcomes.

| No. Patients<br>Randomized | Study Groups                                                                  | Stratification | Significance<br>Demonstrated  | % Change Identified<br>in Trial                                             |
|----------------------------|-------------------------------------------------------------------------------|----------------|-------------------------------|-----------------------------------------------------------------------------|
| 128                        | End-to-end<br>anastomosis,<br>n = 64<br>End-to-side<br>anastomosis,<br>n = 64 | None           | Yes, anastomotic<br>stricture | End-to-end anastomosis<br>40% vs End-to-side<br>anastomosis 18% ( $P<.01$ ) |

**Clinical study 12**

Nederlof N, Tilanus HW, Tran TC, et al. End-to-end versus end-to-side esophagogastrostomy after esophageal cancer resection: a prospective randomized study. *Ann Surg* 2011;254(2):226–33.

**Hypothesis** To compare single-layered hand-sewn cervical ETS anastomosis with ETE anastomosis in a prospective, randomized fashion.

**Published abstract**

**Background** The preferred organ used for reconstruction after esophagectomy for cancer is the stomach. Previous studies attempted to define the optimal site of anastomosis and anastomotic techniques. However, anastomotic stricture formation and leakage remain an important clinical problem.

**Methods** From May 2005 to September 2007, 128 patients (64 in each group) were randomized between ETE and ETS anastomosis after esophagectomy for cancer with gastric tube reconstruction. Routine contrast swallow studies and endoscopy were performed. Anastomotic stricture within 1 year, requiring dilatation, was the primary endpoint. Secondary endpoints were anastomotic leak rate and mortality.

**Results** Ninety-nine men and 29 women underwent esophagectomy and gastric tube reconstruction. Benign stenosis of the anastomosis, for which dilatation was

required, occurred more often in the ETE group (40% vs ETS 18%;  $P < .01$ ) after 1 year of follow-up. The overall (clinical and radiologic) anastomotic leak rate was lower in the ETE group (22% vs ETS 41%;  $P = .04$ ). Patients with an ETE anastomosis suffered less often from pneumonia (ETE 17% vs ETS 44%;  $P = .002$ ) and had subsequently significantly shorter in-hospital duration of stay (15 days vs 22 days,  $P = .02$ ). In-hospital mortality did not differ between the groups.

**Conclusion** ETS anastomosis is associated with a lower anastomotic stricture rate, compared with ETE anastomosis. However, prevention of stricture formation was at high costs with increased anastomotic leakage and longer in-hospital stay. This study is registered with the Dutch Trial Registry and carries the ID number OND1317772.

**Editor's summary and comments** This Dutch trial compared ETE versus ETS esophagogastronomy. The primary outcome was anastomotic stricture with secondary endpoints being anastomotic leak rate and mortality. Although anastomotic stricture rate was higher in the ETE group, the anastomotic leak rate, pneumonia and hospital stay duration were lower. Thus, each surgeon will have to evaluate the use of each technique in context for individual patients to minimize short- and long-term complications.

| No. Patients<br>Randomized | Study Groups                       | Stratification | Significance<br>Demonstrated | % Change Identified<br>in Trial            |
|----------------------------|------------------------------------|----------------|------------------------------|--------------------------------------------|
| 20                         | Ghrelin, n = 10<br>Placebo, n = 10 | None           | Yes, caloric intake          | 874 kcal/d vs 605 kcal/d<br>( $P = .015$ ) |

### Clinical study 13

Yamamoto K, Takiguchi S, Miyata H, et al. Randomized phase II study of clinical effects of ghrelin after esophagectomy with gastric tube reconstruction. *Surgery* 2010;148(1):31–8.

**Hypothesis** Ghrelin ameliorates the postoperative decrease of oral food intake and body weight.

### Published abstract

**Background** Ghrelin is a peptide hormone with pleiotropic functions, including stimulation of growth hormone secretion and appetite, and its levels decrease after esophagectomy. The aim of this study was to evaluate whether exogenous ghrelin administration can ameliorate the postoperative decrease of oral food intake and body weight, which are serious complications after esophagectomy.

**Methods** This prospective, randomized, placebo-controlled clinical trial assigned a total of 20 patients with thoracic esophageal cancer who underwent radical operation into either a ghrelin (n = 10) or placebo (n = 10) group. Synthetic human ghrelin (3 µg/kg) or 0.9% saline placebo was administered intravenously twice daily for 10 days from the day after the start of food intake. The primary endpoint was calories of food intake. Comparison of appetite and changes in weight and body composition were also made between the 2 groups.

**Results** Intake of food calories was greater in ghrelin group than placebo group (mean 874 kcal/d vs 605 kcal/d;  $P = .015$ ). The appetite score tended to be greater in ghrelin group than placebo group ( $P = .094$ ). Loss of weight was less in ghrelin group (–1% vs –3%;  $P = .019$ ) and this attenuation was due largely to a decrease

of lean body weight loss (0% vs -4%;  $P = .012$ ). No side effects were observed in either groups.

**Conclusion** These preliminary results suggest that the administration of ghrelin after esophagectomy increased oral food intake and attenuated weight loss together with maintenance of lean body weight.

**Editor's summary and comments** This prospective, randomized, placebo-controlled clinical trial assigned a total of 20 patients with thoracic esophageal cancer after esophagectomy to receive ghrelin or placebo. Preliminary results suggest that ghrelin increases caloric intake and attenuates weight loss.

| No. Patients<br>Randomized | Study Groups                                                        | Stratification | Significance<br>Demonstrated  | % Change Identified<br>in Trial |
|----------------------------|---------------------------------------------------------------------|----------------|-------------------------------|---------------------------------|
| 79                         | Twice daily proton<br>pump inhibitors,<br>n = 39<br>Placebo, n = 40 | None           | Yes, anastomotic<br>stricture | 13% vs 45% ( $P = .001$ )       |

**Clinical study 14**

Johansson J, Oberg S, Wenner J, et al. Impact of proton pump inhibitors on benign anastomotic stricture formations after esophagectomy and gastric tube reconstruction: results from a randomized clinical trial. *Ann Surg* 2009;250(5):667-73.

**Hypothesis** The use of proton pump inhibitors (PPIs) reduced the prevalence of benign anastomotic strictures after uncomplicated esophagectomies with gastric tube reconstruction and circular stapled anastomoses.

**Published abstract**

**Background** Benign anastomotic strictures are associated with anastomotic leaks or conduit ischemia. Also, patients without those complications develop benign anastomotic strictures. We hypothesize that patients without postoperative anastomotic complications may develop benign anastomotic strictures owing to exposure of acid gastric tube contents to the anastomotic area, and that the formation of such strictures may be reduced by prophylactic use of PPIs.

**Methods** Eighty patients without preoperative chemotherapy or radiotherapy and without clinical or radiologic signs of anastomotic leaks were included in this clinical trial. The patients were randomized to twice daily PPIs or no treatment for 1 year. Benign anastomotic strictures were defined as anastomotic narrowing not allowing a standard diagnostic endoscope to pass without dilatation. The study was registered in the EudraCT database (2009-009997-28) for clinical trials.

**Results** Seventy-nine patients were evaluated. Benign anastomotic strictures developed in 5 of 39 patients (13%) in the PPI group and in 18 of 40 (45%) in the control group (relative risk, 5.6; 95% CI, 2.0-15.9;  $P = .001$ ). The use of a narrower 25-mm cartridge as compared with a wider 28- or 31-mm cartridge significantly increased stricture formations (relative risk, 2.9; 95% CI, 1.1-7.6;  $P = .025$ ).

**Conclusions** Prophylactic PPI treatment reduced the prevalence of benign anastomotic strictures after esophagectomy with gastric tube reconstruction and circular

stapled anastomoses. Larger sized circular staple cartridges additionally reduced the stricture prevalence.

**Editor's summary and comments** This randomized clinical trial studied whether twice daily PPI use may decrease the risk of benign anastomotic strictures. Twice daily PPI use had a lower rate of stricture formation, as was using a wide 28- or 31-mm cartridge instead of the narrower 25-mm cartridge.

| No. Patients Randomized | Study Groups                                               | Stratification | Significance Demonstrated | % Change Identified in Trial  |
|-------------------------|------------------------------------------------------------|----------------|---------------------------|-------------------------------|
| 53                      | Eicosapentaenoic acid enriched, N = 28<br>Standard, n = 25 | None           | Yes, fat-free mass        | 0 kg vs 1.9 kg ( $P = .030$ ) |

### **Clinical study 15**

Ryan AM, Reynolds JV, Healy L, et al. Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg* 2009;249(3):355–63.

**Hypothesis** EPA-enriched EN preserves lean body mass better than standard EN.

### **Published abstract**

**Background** Esophagectomy represents an exemplar of controlled major trauma, with marked metabolic, immunologic, and physiologic changes as well as an associated high incidence of complications. EPA-enriched EN modulates immune function and limits catabolism in patients with advanced cancer, but its impact in the perioperative period is unclear.

**Objectives** To examine the effects of perioperative EPA-enriched EN on the metabolic, nutritional, and immunoinflammatory response to esophagectomy, and on postoperative complications.

**Methods** In a double-blind design, patients were randomized to a standard EN formula or a formula enriched with 2.2 g EPA per day for 5 days preoperatively (orally) and 21 days postoperatively (jejunostomy). Segmental bioelectrical impedance analysis was performed preoperatively and on postoperative day 21. Postoperative complications were monitored, as well as the acute phase response, coagulation markers, and serum cytokines.

**Results** Fifty-three patients (28 EPA, 25 standard) completed the study, and both groups were well matched. Serum and peripheral blood mononuclear cell membrane EPA levels were increased significantly in the EPA group. There was no difference in the incidence of major complications. The EPA group maintained all aspects of body composition postoperatively, whereas patients in the standard EN group lost significant amounts of fat-free mass (1.9 kg;  $P = .030$ ) compared with the EPA group (leg, 0.3 kg [ $P = .05$ ]; arm, 0.17 kg [ $P = .01$ ]; and trunk, 1.44 kg [ $P = .03$ ]). The EPA group had a significantly ( $P < .05$ ) attenuated stress response for tumor necrosis factor alpha, IL-10, and IL-8 compared with the standard group.

**Conclusions** EPA-supplemented early EN is associated with preservation of lean body mass after esophagectomy compared with a standard EN. These properties

may merit longer-term study to address its impact on recovery of function and quality of life in models of complex surgery or multimodal cancer treatment regimens.

**Editor’s summary and comments** EPA-enriched EN was compared with standard EN and found to preserve fat-free mass better than standard nutrition and significantly attenuated stress response.

**Clinical study 16**

Mistry RC, Vijayabhaskar R, Karimundackal G, et al. Effect of short-term versus prolonged nasogastric decompression on major postesophagectomy complications: a parallel-group, randomized trial. Arch Surg 2012;147(8):747–51.

| No. Patients<br>Randomized | Study Groups                                                                                   | Stratification | Significance<br>Demonstrated                    | % Change<br>Identified<br>in Trial |
|----------------------------|------------------------------------------------------------------------------------------------|----------------|-------------------------------------------------|------------------------------------|
| 150                        | Nasogastric tube removed after 6–10 d, n = 75<br>Early removal of the nasogastric tube, n = 75 | None           | Yes, pulmonary complications, anastomotic leaks | 13% vs 45% (P = .001)              |

**Hypothesis** Early removal of the NGT would not adversely affect major pulmonary complications and anastomotic leak rates.

**Published abstract**

**Background** Controversy exists over the need for prolonged nasogastric decompression after esophagectomy. We hypothesized that early removal of the NGT would not adversely affect major pulmonary complications and anastomotic leak rates.

**Methods** This single-center, parallel-group, open-label trial randomized participants 1:1 at a tertiary referral cancer center with high esophagectomy volume. One hundred fifty patients undergoing esophagectomy with gastric tube reconstruction were included. Patients were randomized to conventional nasogastric decompression for 6 to 10 days (75 patients) or early removal (48 hours) of NGT (75 patients) with stratification for pyloric drainage and anastomotic technique. The primary (composite) endpoint was the occurrence of major pulmonary complications and anastomotic leaks. Secondary endpoints were the need for NGT reinsertion and patient discomfort scores. Analysis was performed on an intent-to-treat basis.

**Results** No differences were seen in the occurrence of the composite primary endpoint of major pulmonary and anastomotic complications between the delayed (14 of 75 patients [18.7%]) and early (16 of 75 patients [21.3%]) removal groups, respectively (P = .84). NGT reinsertion was required more often (early 23 of 75 patients [30.7%] vs late 7 of 75 patients [9.3%]) in the early group (P = .001). Mean patient discomfort scores were significantly higher in the delayed (+1.3; 95% CI, 0.4–2.2; P = .006) than in the early removal group. Significantly more patients in the delayed removal group (26 of 75 patients [34.7%] vs 10 of 75 patients [13.3%] in the early removal group; P = .002) identified the NGT as the tube causing the most discomfort.

**Conclusions** Early removal of the NGT does not increase pulmonary or anastomotic complications after esophagectomy. Patient discomfort can be reduced significantly by early removal of the NGT.

**Editor's summary and comments** Early removal of NGT does not increase pulmonary or anastomotic complications. Removal at 48 hours is a feasible choice in the postoperative setting for patient comfort.

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